# BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

## IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.**

STATEMENT DUE 14.6.01

EPA/EPO/OEB
D-80298 München
+49 89 2399 - 0
TX 523 656 epmu d
FAX +49 89 2399 - 4465

Europäisches Patentamt | European Patent Office | Office européen des brevets

Generaldirektion 2 | Directorate General 2 | Direction Générale 2

Mercer, Christopher Paul
Carpmaels & Ransford
43, Bloomsbury Square
London WC1A 2RA
GRANDE BRETAGNE



| Application No. / Patent No. | Ref. | Date |
|---|---|---|
| 90 903 576.8-2116 / 0451216 / 04 | 000945EP/CPM/EK | 14.02.2001 |
| Proprietor: PROTEIN DESIGN LABS, INC. | | |

**Interlocutory decision in Opposition proceedings (Articles 102(3) and 106(3) EPC)**

The Opposition Division - at the oral proceedings dated 20.03.2000 - has decided:

**Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the Convention.**

The reasons for the decision are enclosed.

Documents for the maintenance of the patent as amended:

Text for the Contracting States:
AT BE CH LI DE ES FR GB IT LU NL SE

**Description, pages:**

| | | | | |
|---|---|---|---|---|
| 1,2,4,6,8-13 | of the patent specification | | | |
| 3,5,7 | as received on | 14.06.2000 | with letter of | 12.06.2000 |

**Claims, No.:**

| | | | | |
|---|---|---|---|---|
| 1-13 | as received on | 17.12.1999 | with letter of | 17.12.1999 |

**Drawings, No.:**

| | |
|---|---|
| 1-10 | of the patent specification |

**Comments:**

In the letter dated 17.12.99, this auxiliary request was originally designated "5th

**Registered letter with advice of delivery**

auxiliary request", but has been renumbered in the letter dated 16/03/00 to become "3rd auxiliary request"

**Possibility of appeal**
This decision is open to appeal. Attention is drawn to the attached text of Articles 106 to 108 EPC.

**Opposition Division:**

| | |
|---|---|
| **Chairman:** | WEAVER M R |
| **2nd Examiner:** | HOESEL H R |
| **1st Examiner:** | GOETZ M E |

Ormerod, A
**Formalities Officer**
Tel. No.: +49 89 2399-8164

Enclosure(s): 53 page(s) reasons for the decision (Form 2916)
Wording of Articles 106 - 108 (Form 2019)
Documents relating to the amended text
[ ] Minutes of oral proceedings
Annex A comprising the complete list of documents submitted during the Proceedings

to EPO postal service: 07.02.2001

**Registered letter with advice of delivery**
EPO Form 2327 11.99CSX

# Table of contents

# I. Summary of Facts and submissions

## A Submissions made by the parties during the written phase of the opposition procedure

1. European patent EP-B-0 451 216, based on previous international application WO90/07861 (corresponding European application number 90903576.8), and claiming priority of 28/12/88 (US290 975, "PDL1 application") and 13/02/89 (US310 252, "PDL2 application"), was granted on 24/01/96 to **Protein Design Labs, Inc.** (the Proprietor) with the following claims *inter alia*:

Claim 1:

"The use of at least one amino acid substitution outside of complementarity determining regions (CDR's) as defined by Kabat et al (*"Sequences of Proteins of Immunological Interest", Kabat, E., et al., US Department of Health and Human Services, (1983)*) together with Chothia et al (*Chothia and Lesk, J. Mol. Biol., 196:901-917 (1987)*) in the production of a humanized immunoglobulin, wherein said amino acid substitution is from the non-CDR variable region of a non-human donor immunoglobulin, and in which humanized immunoglobulin the variable region amino acid sequence other than the CDR's comprises at least 70 amino acid residues identical to an acceptor human immunoglobulin variable region amino acid sequence, and the CDR's are from the variable region of said non-human donor immunoglobulin."

Claim 7:

"A method of producing a humanized immunoglobulin chain having a framework region from a human acceptor immunoglobulin and complementarity determining regions (CDR's) from a donor immunoglobulin capable of binding to an antigen, said method comprising substituting at least one non-CDR framework amino acid of the acceptor immunoglobulin with a corresponding amino acid from the donor immunoglobulin at a position in the immunoglobulins where:

(a) the amino acid in the human framework region of the acceptor immunoglobulin is rare for said position and the corresponding amino acid in the donor immunoglobulin is common for said position in human immunoglobulin sequences; or
(b) the amino acid is immediately adjacent to one of the CDR's; or
(c) the amino acid is predicted to have a side chain atom capable of interacting with the antigen or

with the CDR's of the humanized immunoglobulin."

Claim 11:

"A humanized immunoglobulin chain obtainable by a use according to any one of claims 1 to 6."

Claim 12:

"A humanized immunoglobulin chain obtainable by a method according to any one of claims 7 to 10."

2. Notices of opposition were filed by the following Opponents:

| Name | Designation | Opposition with letter dated |
|---|---|---|
| **Medical Research Council** | Opponent 1 | 23/09/96 |
| **Icos Corporation** | Opponent 2 | 01/10/96 |
| **Novartis AG** | Opponent 3 | 08/10/96 |
| **Celltech Therapeutics Ltd** | Opponent 4 | 24/10/96 |
| **Bayer AG** | Opponent 5 | 23/10/96 |
| **Chiron Corporation** | Opponent 6 | 21/10/96 |
| **SmithKline Beecham** | Opponent 7 | 23/10/96 |
| **Genentech Inc.** | Opponent 8 | 23/10/96 |
| **IDEC Pharmaceuticals Corp.** | Opponent 9 | 24/10/96 |
| **Biotest Pharma GmbH** | Opponent 10 | 22/10/96 |
| **Biotransplant Inc.** | Opponent 11 | 24/10/96 |
| **Bristol-Myers Comp.** | Opponent 12 | 24/10/96 |
| **Glaxo group Ltd.** | Opponent 13 | 23/10/96 |
| **Boehringer Ingelheim GmbH** | Opponent 14 | 24/10/96 |
| **Merck Patent GmbH** | Opponent 15 | 21/10/96 |
| **Chugai Seiyaku Kabushiki Kaisha** | Opponent 16 | 23/10/96 |
| **Schering Corp.** | Opponent 17 | 22/10/96 |
| **Ixsys Inc.** | Opponent 18 | 24/10/96 |

The Opponents requested the revocation either of the patent in toto or only of some of the claims as granted and based their requests on the grounds for opposition as set forth below:

**Addition of subject-matter going beyond the application as originally filed (Art. 100(c), 123(2) and (3) EPC)**

| | | |
|---|---|---|
| Opponent 1 | objection raised against | claims 1, 7 |
| Opponent 2 | ---- " ---- | claims 1, 7 and claims dependent thereupon |
| Opponent 4 | ---- " ---- | claims 1, 5, 6 and claims dependent thereupon |
| Opponent 5 | ---- " ---- | claims 1, 5 - 21 |

| | | |
|---|---|---|
| Opponent 7 | ---- " ---- | claims 1, 11, 12, 17 |
| Opponent 8 | ---- " ---- | claims 1 - 21 |
| Opponent 9 | ---- " ---- | claims 1 - 6, 11, 13 - 21 |
| Opponent 10 | ---- " ---- | claims 1 - 21 |
| Opponent 11 | ---- " ---- | claim 1 |
| Opponent 12 | ---- " ---- | claims 1 - 21 |
| Opponent 13 | ---- " ---- | claims 1 - 21 |
| Opponent 15 | ---- " ---- | claims 1 - 6, 11, 13 - 21 |
| Opponent 16 | ---- " ---- | claim 1 |
| Opponent 17 | ---- " ---- | claim 1 |

**No patentable invention has been made (Art. 100(a) and 52 EPC)**

| | | |
|---|---|---|
| Opponent 7 | objection raised against | claims 1, 11 |

**Lack of novelty (Art. 100(a) and 54 EPC)**

| | | |
|---|---|---|
| Opponent 1 | objection raised against | claims 1, 5, 6 - 21 |
| Opponent 2 | ---- " ---- | claims 1, 5 - 7, 9, 11, 13, 14 - 18, 20 |
| Opponent 3 | ---- " ---- | claims 1, 5 - 9, 11 - 17 |
| Opponent 4 | ---- " ---- | claims 1, 5 - 21 |
| Opponent 5 | ---- " ---- | claims 1, 5 - 7, 11 - 18 |
| Opponent 6 | ---- " ---- | claims 1, 7 |
| Opponent 7 | ---- " ---- | claims 1 - 21 when PRIO is invalid |
| | ---- " ---- | claims 1, 7, 11 - 13 when PRIO is invalid |
| Opponent 8 | ---- " ---- | claims 1, 6 - 9, 11 - 19, 21 |
| Opponent 9 | ---- " ---- | claims 1 - 21 when PRIO is invalid |
| Opponent 10 | ---- " ---- | claims 1 - 21 |
| Opponent 11 | ---- " ---- | claims 1, 7 |
| Opponent 12 | ---- " ---- | claims 1, 6 - 9, 11 - 21 |
| Opponent 13 | ---- " ---- | claims 1, 5, 11, 13 - 18 |
| Opponent 14 | ---- " ---- | claims 1, 5, 7, 8, 10 - 17 |
| Opponent 15 | ---- " ---- | claims 1, 6 - 9, 11 - 21 |
| Opponent 16 | ---- " ---- | claims 1, 7 |
| Opponent 18 | ---- " ---- | claims 1, 7 |

**Lack of inventive step (Art. 100(a) and 56 EPC)**

| | | |
|---|---|---|
| Opponent 1 | objection raised against | claims 1, 5, 6, 7, 9, 11 - 21 |
| Opponent 2 | ---- " ---- | claims 1 - 21 |
| Opponent 3 | ---- " ---- | claims 1, 5 - 9, 11 - 21 |
| Opponent 4 | ---- " ---- | claims 1 - 21 |
| Opponent 5 | ---- " ---- | claims 1 - 21 |
| Opponent 6 | ---- " ---- | claims 1 - 21 |
| Opponent 8 | ---- " ---- | claims 1, 3 (when dependent on claim 1), 5, 20 |
| Opponent 9 | ---- " ---- | claims 1 - 21 |
| Opponent 10 | ---- " ---- | claims 1 - 21 |
| Opponent 11 | ---- " ---- | claims 1 - 21 |
| Opponent 12 | ---- " ---- | claims 1, 7 |
| Opponent 13 | ---- " ---- | claims 1 - 21 |
| Opponent 14 | ---- " ---- | claims 1 - 21 |
| Opponent 15 | ---- " ---- | claims 1 - 21 |
| Opponent 16 | ---- " ---- | claims 1 - 21 |
| Opponent 17 | ---- " ---- | claims 1 - 21 |

| | | |
|---|---|---|
| Opponent 18 | ---- " ---- | claims 1 - 7, 10 - 21 |

**Lack of entitlement to priority**

| | | |
|---|---|---|
| Opponent 1 | objection raised against | claims 1, 7 |
| Opponent 3 | ---- " ---- | claims 1, 7 and claims dependent thereupon |
| Opponent 4 | ---- " ---- | claims 1, 5 - 21 |
| Opponent 5 | ---- " ---- | claims 1, 7 and claims dependent thereupon |
| Opponent 7 | ---- " ---- | claims 1, 11 |
| Opponent 8 | ---- " ---- | claims 1, 5 - 9, 11 - 21 |
| Opponent 9 | ---- " ---- | claims 1 - 21 |
| Opponent 10 | ---- " ---- | claims 1 - 21 |
| Opponent 11 | ---- " ---- | claim 1 |
| Opponent 15 | ---- " ---- | claims 1 - 21 (first claimed priority date) |

**Insufficient disclosure (Art. 100(b) and 83 EPC)**

| | | |
|---|---|---|
| Opponent 2 | objection raised against | claims 1 - 21 |
| Opponent 3 | ---- " ---- | claims 1, 7 and claims dependent thereupon |
| Opponent 4 | ---- " ---- | claims 1, 7, 19 |
| Opponent 5 | ---- " ---- | claims 1, 7, 19 |
| Opponent 7 | ---- " ---- | claims 1, 11 |
| Opponent 8 | ---- " ---- | claims 19, 21 |
| Opponent 10 | ---- " ---- | claims 1 - 21 |
| Opponent 12 | ---- " ---- | claim 1 |
| Opponent 13 | ---- " ---- | claims 1 - 21 |
| Opponent 16 | ---- " ---- | claims 1, 7 |
| Opponent 18 | ---- " ---- | claims 1 - 21 |

In the event that the Opposition Division should not be in a position to comply with their requests, all 18 Opponents requested that Oral proceedings be scheduled.

Documents **D1 - D87** listed in Annex A to this decision were submitted by the Opponents in their respective statement of opposition.

3. With a letter dated 07/04/98, the Proprietor submitted a first reply to the above oppositions wherein he refutes the arguments brought forward by the Opponents and requests maintenance of the patent as granted. Oral Proceedings were requested in the event that the Opposition Division should not be in a position to comply with his request.

Documents **D88 - D102** listed in Annex A were submitted by the Proprietor in support of his position.

4. Observations were made by the third party "Buzz Lightyear" on 12/05/98 and 07/12/99. Following the EPO's practice as set out in the Formalities Officer's letter to the Proprietor dated 18/06/98, these observations were considered to be acceptable.

5. On 12/05/99, the invitation to attend Oral Proceedings was sent out, together with an annex setting out the preliminary opinion of the Opposition Division on the issues raised by the Opponents and the Proprietor, as summarized below:

- On the ground "Added subject-matter": claims 1, 2 - 6 and 11 were considered not meet the requirements according to Art. 123(2) EPC. Deletion of the unallowably added subject-matter was considered to result in an unallowable broadening of their scope (Art. 123(3) EPC).
- On the issue "Lack of entitlement to priority": for claims 1 - 6 and 11 no opinion was expressed because of their non-compliance with Art. 123(2)/(3). For claim 7, only the 2nd priority date of 13/02/89 was considered to be validly claimed.
- On the ground "Lack of novelty": for claims 1 - 6 and 11 no opinion was expressed because of their non-compliance with Art. 123(2)/(3). Claims 7, 9, 12 - 17 having an effective date of 13/02/89 (second priority of PDL2 application) were not considered to meet the requirements according to Art. 54(1) - (4) EPC in view of **D36** and **D48**.
- On the ground "Lack of inventive step": the Opposition Division considered it to be obvious to take into consideration any suggestion relating to a possible role of Kabat framework amino acid residues in the antigen binding (**D32, D23, D38, D40**) in the light of the teaching provided by **D36**.
- On the ground "Insufficient disclosure": The granted patent was considered to be in accordance with the requirements pursuant to Art. 83 EPC.
- On the ground "Non-patentable subject-matter": The granted patent was acknowledged to be in accordance with the requirements pursuant to Art. 52(2)(a) - (c) EPC.

Additionally, the decisions of the EPO's Technical Boards of Appeal **D103 - D111** as set out in Annex A were identified.

6. Observations on the preliminary opinion issued by the Opposition Division were submitted by the Proprietor in a letter dated 17/12/99, together with a set of 5 auxiliary requests. In support of his position, the Proprietor further submitted the documents **D112 - D129** as listed in Annex A.

7. Further substantial observations, partly on the preliminary opinion issued by the Opposition Division and partly on the letter of the Proprietor dated 17/12/99, were submitted by:

   - Opponent 4 on 16/12/99, the submission introducing further documents **D130 - D134** as listed in Annex A.

   - Opponent 8 on 17/12/99, 08/03/00 and 13/03/00, the submission introducing further documents **D135 - D141** as listed in Annex A.

   - Opponent 16 on 22/01/99

   - Opponent 17 on 11/02/00

8. With a letter dated 16/03/00, the Proprietor submitted a new set of 3 auxiliary requests, wherein auxiliary requests 1 and 2 were derived from auxiliary requests 3 and 4 as filed on 17/12/99 and auxiliary request 3 was identical with auxiliary request 5 as filed on 17/12/99. Briefly, the amendments made in the set of auxiliary requests are:

   **First auxiliary request**

   - Claim 1 is based on claim 7 as granted, with the following modifications:
     - "Framework" replaced by "**Kabat** framework"
     - The element "**... and wherein at least one of said amino acid substitution is also outside of the first heavy chain hypervariable loop as defined by Chothia et al. [Chothia and Lesk, J. Mol. Biol., 196:901-917 (1987)] ...**" has been added.
   - Claims 2 - 14 are adapted correspondingly, with minor modifications in their wording.

**Second auxiliary request**

- Claim 1 is as in the first auxiliary request, but the amino acid selection criterion is a restricted version of criterion (c) only ("... amino acids having a side chain **capable of interacting with the CDR** ..." instead of "**capable of interacting with the CDR or with the antigen** ...")
- Claims 2 and 3 correspond to claim 1 of the first auxiliary request, but the selection criterion for amino acids are criteria (a) and (b) only.
- Claims 4 - 16 are adapted correspondingly, with minor modifications in their wording.

**Third auxiliary request**

- Claim 1 corresponds to claim 7 as granted, but includes the subject-matter of claim 10 as granted, reciting the specific amino acid sequence of the anti-*Tac* antibody.
- Claims 2 - 13 were adapted correspondingly, with minor modifications in their wording.

9. With letters of 21/12/99, 02/03/00, 17/03/00 and with telefax of 20/03/00, Opponents 1, 7, 16 and 15 withdrew their oppositions; with telefaxes of 08/03/00, 09/03/00, 15/03/00, 10/03/00, and 18/02/00, Opponents 2, 9, 12, 13 and 18 declared that they did not wish to attend the Oral Proceedings.

10. Oral Proceedings were held on 20/03/00. The main request as well as auxiliary requests 1 and 2 were rejected for non-compliance with Art. 123(2) EPC; the patent was maintained on the basis of auxiliary request 3 which was found to comply with the requirements of the EPC.

## B Submissions made by the parties during the Oral Proceedings

After rejection of the main request as well as auxiliary requests 1 and 2 for non-compliance with Art. 123(2) EPC, the Proprietor requested the Opposition Division to set forth the exact reasons for the rejection; he furthermore requested an opportunity to file another auxiliary request which would take into account the said reasons. In reply, some of the Opponents announced that, should the Opposition Division be inclined to accept the Proprietor's requests, they would seek for an adjournment of the Oral Proceedings and an award of costs.

For the reasons set out below, the Opposition Division refused both requests of the Proprietor.

# II. Reasons for the decision

## A The main request - Art. 123(2) and (3) EPC

During prosecution of the case, the following objections were raised by the Opponents:

1. Although claim 1 as granted has the sole technical requirement that *"... at least 70 amino acid residues ..."* of the human acceptor framework be present in **the whole Ig molecule**, such element did not allegedly exist in the application as filed, where it was clearly stated that at least 70 human amino acid should be present **per Ig chain** in a humanized immunoglobulin. As it is known that a complete Ig molecule has four chains, the said requirement in claim 1 would appear to constitute added subject-matter.

   The Opposition Division cannot share this view: the relevant passage in the description of the application as filed reads (page 11/lines 3 - 7)

   > *"As used herein, a "human-like framework region" is a framework region that in each existing chain comprises at least about 70 or more amino acid residues, typically 75 to 85 or more residues, identical to those in a human immunoglobulin."*

   However, claim 1 also states that in the humanized immunoglobulin which it is desired to protect

   > *"... the **variable region** amino acid sequence other than the CDR's comprises at least 70 amino acid residues identical to an acceptor human immunoglobulin **variable region** amino acid sequence, ....";*

   and therefore clearly indicates that the occurrence of 70 amino acid residues is not a technical feature of the whole immunglobulin molecule, but that it relates to each variable region amino acid sequence, **such variable region occurring in each of the 4 chains constituting an immunglobulin molecule.**

This would appear to correlate perfectly with the Proprietor's definition of an immunglobulin, which includes single heavy or light chains, see page 10/lines 10 - 24 of the application as filed.

Hence, it is considered that the *"... at least 70 amino acid residues ..."* feature of claim 1 as granted does not constitute an addition of previously undisclosed subject-matter.

2. Whereas claim 22 as originally filed related to *"A Humanized immunoglobulin designed according to claims 18, 19 or 20"*, the Opponents noted that the corresponding claims 11 and 12 of the patent used the term *"obtainable by"* instead of *"designed"*. This would allow for the claimed humanized immunoglobulin to be produced by other methods than the methods of claims 1 - 10 (to which claims 11 and 12 refer), said methods clearly not having been disclosed in the application as filed.

However, as correctly pointed out by the Proprietor, it is not appropriate to stipulate that the scope of claims to be granted should not be broader than the scope of the claims as originally filed; indeed, Art. 123(2) EPC only prescribes that an application may not be amended in such a way that it contains subject-matter extending beyond the content of the application (claims, description, drawings) as filed.

Claims 11 and 12 find ample support in the description as originally filed, see e.g. page 4/lines 1 - 36 (note the use of the terms *"may"* and *"can"* in the characterization of the immunoglobulins of the application), page 6/lines 21 - 26 and page 9/lines 2 - 5. Moreover, the structure of the immunoglobulins according to the alleged invention is defined in method claims 1 - 6 and 7 - 10; claims 11 and 12 are product claims which merely refer to the immunoglobulins defined in the method claims, independently of the production method.

Hence, the specification as originally filed (description, claims and drawings) is considered by the Opposition Division to provide sufficient substantial support for the subject-matter of the claims 11 and 12, bearing in mind the common knowledge level of the skilled practitioner.

3. Although claim 1 as granted recites *"... at least one amino acid substitution ..."* outside of CDRs without any further limitation, the Opponents have argued that the same technical feature has always been linked in the application as originally filed to certain criteria according to which an amino acid residue must be selected for substitution. Thus, claim 19 as originally filed would clearly teach that at least one human framework amino acid can be substituted **when and only when** it meets one of criteria (a) to (c) as further set forth in claim 19. This would appear to be confirmed by the passage bridging pages 5 and 6 of the application as filed.

Moreover, it would appear that the wording *"... at least one amino acid substitution ..."*, as used in granted claim 1 and on page/lines 14 - 20, unallowably adds subject-matter because the application as filed does not disclose the production of a humanized immunoglobulin with less than 3 amino acid substitutions, such as e.g. an Ig molecule where only 1 amino acid residue has been substituted.

The Opposition Division cannot share this view: it should be pointed out that the technical element of granted claim 1, *"... at least one amino acid substitution outside of CDRs ... in the production of a humanized immunoglobulin, ..."* is supported by claim 11 (page 35/lines 14 - 19) and claim 19 as originally filed (page 36/lines 27 and 28),

> *"... said method comprising the steps of substituting **at least one** amino acid of the acceptor immunoglobulin ..."*,

and the statement made on page 5, lines 32 - 36 of the description as filed.

Contrary to the view expressed by some of the Opponents, the statement of page 5, lines 32 - 36 of the description as filed would have been interpreted by the skilled person as a "stand-alone" description of a preferred embodiment relating to the substitution of amino acids as such, without an immediate link to technical selection criteria. Indeed, the next sentence starts with *"More specifically, ..."*, indicating that the following statement relates to the <u>further</u>, restricted embodiment of selecting the amino acid residues to be substituted by following criteria (a) - (c) as set out on page 6/lines 3 - 13.

Hence, the specification as originally filed is considered by the Opposition Division to provide sufficient substantial support for the *"... at least one amino acid substitution ..."* feature of claim 1 as granted.

4. Although claim 7 as granted recites substitution criterion (c) as comprising the sole technical requirement that the amino acid should have a side chain atom capable of interacting with the antigen or with the CDRs of the humanized immunoglobulin, the Opponents stated that, in the application as filed, the same criterion (c) was mandatorily linked to the technical element of the same amino acid being also *"... within about 3 Å of the CDRs ..."*, as seen from page 6 / lines 10 - 13, page 14 / lines 14 - 25 and claim 19. Omission of the latter feature in claim 7 as granted was therefore seen as a violation of Art. 123(2) EPC.

As demonstrated by the Proprietor in the letter dated 07/04/98, page 13, said objection is considered to be without merit.

Indeed, in the Opposition Division's view, the omission of the technical element *"... within about 3 Å of the CDRs ..."* from original claim 19, now claim 7, does not contravene Art. 123(2) EPC, as the description as filed, in the explanation of "Criterion IV" on page 14, already clearly pointed out that the said element is merely a secondary feature of the main criterion telling the reader that certain amino acids have been shown to have the capability of interacting with the antigen or the CDR via certain mechanisms.

Indeed, page 14, lines 21 - 25 of the description as filed read

> *"Amino acids according to this criterion will **generally** have a side chain within about 3 Ångstrom units ... and must contain atoms that could interact ...",*

(emphasis added), thereby indicating that the second criterion, *"... side chain containing atoms that could interact ..."* is obligatory, whereas the first criterion, *"... within about 3 Å ..."* does not necessarily apply, a view which appears to be supported by the experimental details given for the humanized anti-*Tac* antibody, see page 26/lines 35 - 38 and page 27/lines 15 - 16 of the description as filed.

5. Although claim 1 as granted recites that *"... said amino acid substitution is from the non-CDR variable region of a non-human donor immunoglobulin, ..."*, some Opponents alleged that the original application did not provide such basis for claiming any possible donor sequence with the exeption of human sequences. Indeed, it would appear that the application as filed disclosed only murine donor sequences, as e.g. seen from page 4/lines 16 - 20 and page 5/lines 34 - 36, such murine sequences not constituting an adequate support for an extension of this technical element to *"non-human"* (i.e. comprising any other animal with the exception of humans) sequences.

This objection must already fail in view of the technical principle underlying the claimed subject-matter, as set out throughout the whole application as filed. It is clear to any skilled person that humanized antibodies can only be prepared by grafting foreign (i.e., non-human) stretches of amino acids onto a human acceptor framework, as explained on e.g. page 5/lines 8 - 12 of the application as filed:

> *"The present invention also provides novel methods for designing human-like immunoglobulin chains having one or more complementarity determining regions (CDR's) from a donor immunoglobulin and a framework region from a human immunoglobulin ..."*

This passage clearly does not restrict the donor sequences to amino acid stretches selected from murine antibodies, which is only a preferred embodiment of the claimed subject-matter, as can be seen from e.g. page 4 lines 20 - 23, reading

> *"**For example**, mouse complementarity determining regions, with or without additional naturally-associated mouse amino acid residues, can be used ..."*

Hence, it is considered that the use of a sequence selected from a *"... non-human donor immunoglobulin ..."* is disclosed in the application as originally filed.

6. All Opponents have vigorously attacked the patent as granted under Art. 123(2) EPC on the ground that claim 1 comprises the Proprietor's own definition of a complementarity determining region (CDR),

> *"... complementarity determining regions (CDR's) as defined by Kabat et al ("'Sequences of Proteins of Immunological Interest", Kabat, E., et al., US Department of Health and Human Services, (1983)) together with Chothia et al (Chothia and Lesk, J. Mol. Biol., 196:901-917 (1987)) in the production of a humanized immunoglobulin, ...".*

More particularly, the Opponents objected to the use of the term *"together with"* linking the two references to prior art documents containing the two alleged definitions of CDRs, as the application as filed did not provide any basis for such additive re-definition, which conferred CDR1 (the complementarity determining region of an antibody's heavy chain variable region) the meaning of a stretch of amino acids extending from residue 26 to residue 35. Indeed, as explained in the Proprietor's submissions, the aim of such proprietary definition of CDRs was clearly to distinguish claim 1 (and claim 7) from document **D36**, wherein *Riechmann et al.* disclose a reshaped antibody comprising CDRs of rat antibody YTH 34.5HL on a human framework, and where intentional Ser27 ---> Phe27 and Ser30 ---> Thr30 framework substitutions were made.

a) Preliminary remark

It is quite clear that the incorporation of Applicant's proprietary CDR definition into claim 1 as granted, *"CDRs as defined by Kabat (...) together with Chothia (...)"*, can by no means be discussed under the mere aspect of "simple addition of a reference to the prior art" as alleged by the Proprietor. Since, depending on its interpretation, it is suitable to substantially modify the scope of the claims (amino acid residues 26 - 30 included in CDR1 of the heavy chain or not) **and** the relevance of previously published documents such as **D36**, the said definition must be considered to be a relevant technical feature of the claimed subject-matter.

In this context, attention is drawn to the fact that the incorporation of the feature "*Chothia* definition of CDRs", as allegedly disclosed in prior art

document **D28**, into claim 1 (in an additive manner to the scientifically accepted definition provided by *Kabat*, see paragraphs d1) - d6) below) does not comply with the rules set out for such incorporation in EPC Guidelines C-VI, 5.7d. Indeed, at least rule (i) given in the Guidelines is not complied with, as it was not undoubtly clear that, from the simple citation of the *Chothia* document on page 10/lines 5 - 6 of the application as filed, protection was possibly sought for any feature comprised in the said document.

b) As argued by the Proprietor, the alleged basis for his own definition of a CDR is the unique part of the application as filed which relates to CDR definitions and which is on page 9/line 37 - page 10/line 9:

> *"The variable regions of each light/heavy chain pair form the antibody binding site. The chains all exhibit the same general structure of relatively conserved framework regions joined by three hypervariable regions, also called CDRs (see, "Sequences of Proteins of Immunological Interest," Kabat, E., et al., U.S. Department of Health and Human Services, (1983); and Chothia and Lesk, J. Mol. Biol., 196:901-917 (1987), which are incorporated herein by reference)".*

The two references mentioned here, *Kabat et al.* and *Chothia et al.*, correspond to documents **D15** and **D28**, respectively.

On the basis of this originally disclosed passage, the text portions on page 3 of the patent comprising lines 7 - 25 and lines 29 - 36 have been included in the description; furthermore, a new claim 1 has been submitted for substantive examination, ultimately resulting in claim 1 as granted, comprising the Applicant's own definition of CDR1 of the heavy chain as extending from residues 26 - 35.

c) The arguments set forth by the Opponents clearly followed two lines:

Objection 1: Neither the application documents as filed (explicitly) nor the state of the art available at the priority date of the subject-matter of claim 1 (implicitly, by way of the reference to documents **D15** and **D28**) provided a basis for a combined

"*Kabat* and *Chothia*" definition of CDRs, because *Chothia* **had not attempted to define CDRs**. In such case, violation of Art. 123(2) EPC would have to be seen in the addition of a new technical teaching for which no scientific support whatsoever would exist.

Objection 2: Assuming, *arguendo*, that a technical basis for a combined "*Kabat* and *Chothia*" CDR definition were to exist, the wording of the sole passage quoting **D15** and **D28**, together with the remainder of references to *"CDR"* or *"Framework"* amino acid residues in the application as filed, would not allow for an **additive combination** of a CDR as defined by *Kabat* in D15 (extending from residues 31 - 35 of the $V_H$ chain) with a CDR as defined by *Chothia* in D28 (extending from residues 26 - 32 of the $V_H$ chain) into a "new" CDR as defined by the Proprietor (extending from residues 26 - 35 of the $V_H$ chain).

d) Concerning objection 1:

It has to be decided whether *Chothia et al.* have made an attempt to provide **an alternative or refined definition** of the CDR definition given by *Kabat et al.* and, if so, whether the skilled person would have acknowledged that such redefinition had been made.

Having analysed the considerable amount of arguments and evidence, mainly in the form of sworn declarations made by eminent scientists, which has been submitted by the Proprietor and the Opponents to support their case, the Opposition Division has come to the conclusions as set forth below.

d1) A redefinition of *Kabat* CDRs by *Chothia* ?

Document **D97**, submitted by the Proprietor, provides what appears to be a clue to a correct interpretation:

*"The 27-30th and 94th residues of $V_H$ framework's of mouse B-B10 were also grafted, since these residues were considered to affect the conformation of the CDR's (Chothia and Lesk, 1987 (**D28**); Chothia et al., 1989 (**D29**)).*"

***D97**, page 438*

*"The 27-30th and 94th amino acid residues of humanized B-B10 $V_H$ were grafted from the corresponding amino acid residues of mouse B-B10, despite the fact that these residues belonged to framework's. The framework residues to be reverted were chosen according to Chothia and Lesk, 1987 (**D28**); Chothia et al., 1989 (**D29**) who pointed out that the particular framework residues participated in or had an influence on the formation of correct CDR loops.*"

***D97**, page 442*

The underlined terms in these three citations, i.e. *"the conformation of the CDR's"* and *"CDR loops"* support the Opposition Division's view that CDRs as defined by *Kabat* represent **numbered linear sequences of amino acids** forming the hypervariable regions of an antibody. Parts of the said hypervariable regions may assume a particular three-dimensional conformation and form the **"hypervariable loops"** according to *Chothia*. Hence, basically, as noted in **D97**, the primary CDR structures (*Kabat*) assume a secondary loop conformation (*Chothia*).

The only common element to the *Kabat* and the *Chothia* approach would appear to reside in their attempt to provide a characterization of **hypervariable regions.**

d2) The view adopted by *Kabat et al.*

In their basic document **D7**, they introduce the technical term *"CDR"* to describe the hypervariable regions of an antibody as the amino acid stretches *"making contact with the antigen"*; CDRs are defined in terms of the **variability in their primary amino acid sequence**, based on previous work done by *Wu & Kabat* in **D1**, where the said variability is mathematically defined.

**D7** depicts the 6 CDRs of the light and heavy chain variable region, using the nomenclature

**CDR1 - 3 of $V_L$:** amino acid residues 24 - 34, 50 - 56 and 89 - 97
**CDR1 - 3 of $V_H$:** amino acid residues 31 - 35, 50 - 65 and 95 - 102

The designation *"Framework residues"* is used for all other amino acid residues.
Taking a somewhat extreme position, *Kabat et al.* have not done anything more than to identify and number the hypervariable amino acid residues at the primary structure level of the immunoglobulin. **D15**, **D27** and **D62** repeat this definition (see e.g. **D15**, pages ii, iii, vi and x) and give a tabular overview of published CDRs.

d3) The view adopted by *Chothia et al.*

In **D28**, *Chothia* seeks a characterisation of the hypervariable regions in terms of their three-dimensional structure; to this end, they analyse the amino acid responsible for the **conformation** of hypervariable loops connecting the β-sheet framework of the variable region.

The authors themselves point out that their approach to predicting the three-dimensional structure of the hypervariable loops is different from previous work of scientists having made antibody modelling studies (to which group of scientists *Kabat* also belongs): instead of using the CDR approach (based on linear **sequence variability**), they define the amino acid residues which are responsible for the main chain **conformation**: they find that most of the hypervariable loops have one of a small discrete set of possible main chain conformations (*"canonical structures"*). It turns out that beside residues in the *Kabat* CDRs, also other residues in the *Kabat* framework have influence on the **conformation** of the loops. Hence, five of *Chothia*'s canonical structures are **shorter** and therefore represent a sequence subset of the *Kabat* CDRs (CDR1 - 3 of the light chain, CDR2 and 3 of the heavy chain), one is **overlapping** with *Kabat* CDR1 of the heavy chain.

As a logical consequence of this different approach, *Chothia* never uses the term "CDR" to designate hypervariable loops: instead the nomenclature L1 - L3 (light chain hypervariable loops) and H1 - H3 (heavy chain hypervariable loops) is used, see also the *Chothia* declaration **D84**.

Most importantly, *Chothia* himself has made the strict distinction between *Kabat* CDR's and his hypervariable loops:

> *"Their limits are somewhat different from those of the CDR's defined by Kabat et al. (1983) on the basis of sequence variability: ..."*
>
> **D28**, page 904,

and in **D24**,

> *"The antigen-binding site contains three **hypervariable loops** from $V_L$ and three from $V_H$, denoted L1, L2, L3 and H1, H2, H3 (11). The residues, **numbered according to Kabat** et al. (5), are: ... **[The complementarity determining regions (CDRs), defined by Kabat et al. (5) on the basis of sequence comparisons, are more extensive].**"*
>
> **D24**, page 755

d4) The view adopted by the scientific community

As pointed out by the Proprietor, it is to be recognized that much of the scientific literature published has added a lot of confusion by having interchangeably used two designations for what should have been considered to represent technically different features, i.e. *"CDR1 - 3 of $V_H$ and $V_L$"* as opposed to *"Hypervariable loops H1 - H3 and L1 - L3"*.

Compare for instance, a citation made in **D40**:

> *"... in **CDR1** of the antibody heavy chain which extends from residues 31 to 35 by sequence (Kabat, **D27**) and from residue 26 - 32 in structural terms (Chothia, **D28**) ...",*
>
> ***D40**, page 172*

with the statement given in **D36**:

> *"By sequence, the first hypervariable loop extends from residues 31 - 35 (ref. 25, **D27**), whereas by structure it extends from residues 26 - 32 (ref. 32, **D28**)."*
>
> ***D36**, page 326*

Under the aspect of technical nomenclature, both statements (and any other such statement found in the literature) appear to be inaccurate, as *Kabat* has not defined "loops", but linear amino acid sequences and *Chothia* has never defined CDRs, but hypervariable loops.

It appears that any correct reference to a delineation of hypervariable regions must take into account the existence of two technically distinct approaches:

- "CDR" must be equated to the *Kabat* definition of hypervariable region based on sequence variability and hence always means the **numbered** sequences consisting of residues 24 - 34, 50 - 56 and 89 - 97 (light chain) and residues 31 - 35, 50 - 65 and 95 - 102 (heavy chain);

- "Hypervariable loop" must relate to *Chothia*'s three-dimensional structural considerations of the hypervariable region, including the observation that residues outside of the *Kabat* framework have influence on the **conformation** of the loops.

Such technically accurate references are numerous, see the same document **D40** as above, where it is confirmed that a Ser27 ---> Phe27 mutation made by *Riechmann* in **D36** occurred

> *"... in the antibody 'framework' region, in addition to the CDR replacement steps, ..."*
>
> ***D40**, last 3 lines of page 172, left column,*

see furthermore **D26**, describing that

> *"... The individual β-strands are linked by loops which at one tip of the β-sheet may fashion a binding pocket for small haptens[1,2]. Sequence comparisons among heavy- and light-chain variable domains ( ... ) reveal that each domain has three CDR's flanked by*

*four relatively conserved regions (framework regions)[4]. As seen in the structure of the human myeloma protein NEWM (Fig.1), **the CDRs include each of the three main loops**. ..."*

***D26**, page 522,*

from which statement it is apparent thet the author makes a clear distinction between "CDRs" and "loops",

see **D32**, reading

*"The determination as to what constitutes a CDR and what constitutes a framework region was made on the basis of the amino acid sequences of a number of Igs. However, from the 3-dimensional structure of a number of Igs, it is apparent that the antigen binding site of an Ig variable domain comprises three looped regions supported on sheet-like structures. **The loop regions do not correspond exactly to the CDR's, although in general there is considerable overlap.**"*

***D32**, page 6, last paragraph,*

see **D48**, noting that

*"Although the two changes Ser(27) to Phe and Ser(30) to Thr are located within the **framework region** as defined in reference 11 (**D27**), they lie within the **hypervariable loop H1** as defined in reference 18 (**D28**)."*

***D48**, page 3, lines 40 - 42,*

and see also **D69**, stating *expressis verbis* that

*"The **framework residues 28 - 30** are part of the **H1 hypervariable loop (residues 26 to 32) defined by Chothia & Lesk**."*

***D69**, page 57, bottom of left column,*

In the Opposition Division's view, and although some scientists such as the Declarants nominated by the Proprietor may have a different view, the overwhelming majority of publications referring to CDRs correctly use this term as defined by *Kabat*, i.e. they consider it as a numbering system of linear **sequences** consisting of the hypervariable amino acid residues 24 - 34, 50 - 56 and 89 - 97 (CDRs of the light chain) and residues 31 - 35, 50 - 65 and 95 - 102 of the heavy chain (CDRs of the heavy chain),

see **D10**, page 684/Table 1, **D23**, page 750/Tables 1 and 3, **D32**, page 17/4th paragraph and Figs. 2, 3 and 7, **D36**, page 325/right column/lines 4 - 5 of the section "Strategy" and Fig. 1, **D38**, Fig. 3, **D48**, Figs. 2a and 2b, see also the documents submitted by the Proprietor, **D91**, Fig. 6, **D94**, Figs. 1a, 1b, 2a, 2b and 12, **D96**, Fig. 3.

It is worthy of note that publications having the inventors as co-authors also clearly show that they understand the term "CDR" as defined by *Kabat*, see **D52**, page 10031/right column, Fig. 2 and **D56**, Fig. 1 and Table 1.

Last, but not least, the present inventors also had no difficulties in accepting the *Kabat* CDR definition in the relevant passages of the disputed patent, as will be demonstrated in section d6) below.

d5) Conclusion

There is no convincing evidence for an alternative or refined definition of *Kabat et al.* CDRs by *Chothia et al.*: the latter authors simply establish the concept of the "hypervariable loop" by determining the **residues controlling the 3-dimensional conformation** as opposed to *Kabat*'s definition of a CDR strictly relying on **residues determining the sequence variability**. To this end, *Chothia* accepted the CDR definition of *Kabat* based on sequence hypervariability and merely **compared** his data to the *Kabat* CDR's by, of course, using the *Kabat* numbering system.

What **both** authors have done, is a characterization of hypervariable regions: "CDR" is one technical aspect of hypervariable regions, "hypervariable loop" is the other one.

It follows that, according to the skilled person's understanding of the published prior art at the effective date of the application, the statement

> *"The variable regions of each light/heavy chain pair form the antibody binding site. The chains all exhibit the same general structure of relatively conserved framework regions joined by three hypervariable regions, also called CDRs (see, "Sequences of Proteins of*

*Immunological Interest," Kabat, E., et al., U.S. Department of Health and Human Services, (1983); and Chothia and Lesk, J. Mol. Biol., 196:901-917 (1987), which are incorporated herein by reference)".*

made on page 9 / line 37 - page 10 / line 7 of the application as filed, can by no means be considered to provide a basis for the Proprietor's proprietary definition of CDRs, i.e. equivalent to an additive combination of "CDR" as defined by *Kabat* in **D7** and "loop" according to the *Chothia* document **D28**.

In the light of the relevant prior art as analysed above, the meaning the skilled practitioner would give to this sentence in the original application is clearly that *Kabat* had defined the CDRs on the basis of sequence variability, that *Chothia* had acknowledged this definition and had given a new characterization of **hypervariable regions** by establishing the concept of **hypervariable loops**.

Hence, the reference in claim 1 and the description to *Chothia* (**D28**) as a document defining CDRs is improper and reflects the state of the art in an inaccurate manner; it therefore renders claim 1 unclear (Art. 84 EPC).

d6) The meaning given to "CDR" in the application:

In striking contrast to the signification the Proprietor wishes to attribute to the term "CDR" in claim 1, the remainder of the application as filed is in perfect agreement with *Kabat*'s CDR definition:

- The text portion on page 10/line 37 - page 11/line 3 of the application as filed explains that

  *"As used herein, the term "framework region" refers to those portions of immunoglobulin light and heavy chain variable regions that are relatively conserved (i.e., other than the CDR's) among different immunoglobulins in a single species, as defined by Kabat, et al., op. cit.",*

and therefore defines the *Kabat* framework residues **(with no reference to *Chothia*)** in the commonly accepted technical sense; since page 11/lines 19 - 22 further asserts that

> *"..., also included are criteria by which a limited number of **amino acids in the framework** of a humanlike or humanized immunoglobulin chain are chosen to be the same as the amino acids at those positions in the donor Ig rather than in the acceptor Ig, in order to increase the affinity of an antibody comprising the humanized immunoglobulin chain.",*

this can only mean that amino acid residues in the framework as defined by *Kabat* are to be substituted. However, if the framework is defined according to *Kabat*, the Applicant has implicitly acknowledged the *Kabat* definition of CDRs.

- In the experimental part of the application as filed, the list of 4 selection criteria according to which a human acceptor amino acid at a particular position should be replaced by a non-human donor amino acid comprises a clear acceptance of the *Kabat* CDR definition: at least the light chain CDRs and the crucial CDR1 of the heavy chain are acknowledged to consist of amino acid residues 24 - 34, 50 - 56, 89 - 97 and 31 - 35, as defined by *Kabat* (with no reference to *Chothia*), see e.g. page 26/lines 23 - 26,

> *"At each position, the Eu amino acid was selected for the humanized sequence, unless that position fell in any one of the following categories, in which case the anti-Tac amino acid was selected:*
> *(1) The position fell within a complementarity determining region (CDR), as defined by Kabat, et al., op. cit. **(amino acids 31-35, 50-66, 99-106);"***

and Figs. 1 and 2, wherein the *Kabat* CDRs are underlined.

- From the indication given on page 26/lines 32 - 34 of the application, that amino acid residue 30 of the heavy chain is *"adjacent to a CDR"*, it can only be concluded that CDR1 starts at position 31 and therefore complies with the *Kabat* definition (with no reference to *Chothia*).

e) Concerning objection 2:

Basically following the reasoning set forth by the Third Party and by some Opponents, it may be assumed, *arguendo*, that *Kabat* has defined CDR1 of the heavy chain as being constituted by amino acid residues 31 - 35 and *Chothia* has defined **the same CDR1** as extending from amino acid 26 to amino acid 32.

Clearly, in such a case, the text portion of the description

> *"The variable regions of each light/heavy chain pair form the antibody binding site. The chains all exhibit the same general structure of relatively conserved framework regions joined by three hypervariable regions, also called CDRs (see, "Sequences of Proteins of Immunological Interest," Kabat, E., et al., U.S. Department of Health and Human Services, (1983); and Chothia and Lesk, J. Mol. Biol., 196:901-917 (1987), which are incorporated herein by reference)".*

would then be considered by the skilled person to reflect such an assumption, namely that there existed **two different interpretations of the same entity**, one of them (by *Kabat*) postulating

> **"CDR1 comprises amino acid residues 31 - 35"**

and the other one (by *Chothia*) stating that

> **"CDR1 extends from amino acid residues 26 - 32"**

It goes without saying that the mere provision of a reference to such divergent interpretations (as done in the application by the citation of the two relevant pieces of prior art describing the said interpretations, *Kabat* 1983 and *Chothia* 1987) **does not** however constitute a supporting disclosure of the combination, that is

> **"In this patent , CDR1 comprises amino acid residues 26 - 32 PLUS residues 31 - 35"**

ultimately resulting in the proprietary definition of CDR1 of the heavy chain to comprise amino acid residues 26 - 35. The Proprietor's assertion that such

definition should be accepted because of the fact that the references to the *Kabat* and *Chothia* documents on page 10/lines 4 - 6 of the application as filed are linked by *"and"* instead of *"or"*, is considered to be without merit, as this is merely a linguistic consideration which ignores the fact that in the English language, the listing of several equivalent, optionally applicable alternatives by using the conjunction *"and"*, does not imply that this listing automatically provides the additive information contained in all items of the list.

7. Conclusion as to Art. 123(2) EPC

From the above analysis, the Opposition Division concludes that the feature *"Kabat [...] together with Chothia [...]"* in claim 1 has neither a technically reasonable nor a legal basis in the application documents as filed; claim 1 does not therefore meet the requirements of Art. 123(2) EPC.

This opinion also applies to claims 2 - 6 directly dependent upon claim 1 and to claim 11 reciting humanized immunoglobulins obtainable by the method of claim 1, as well as to any further claim being dependent upon or referring thereto.

This opinion also applies to claim 7 and 12 where no particular definition of the CDR has been given; however, in the absence of such definition, and since it is assumed that the same invention is under consideration, the Proprietor is clearly bound by the definition he has provided in claim 1.

8. Conclusion as to Art. 123(3) EPC

The unallowably extended subject-matter of claim 1 (and claims 2 - 7, 11, 12, as well as any further claim being dependent upon or referring thereto) of the patent excludes a stretch of the human acceptor antibody comprising amino acid residues 26 - 35 from substitution by a murine amino acid; deletion of the extended subject-matter, thereby reverting to the commonly accepted *Kabat* CDR1 definition, would result in a claim only excluding amino acid residues 31 - 35, equivalent to an unallowable broadening of its scope (Art. 123(3) EPC).

**B Auxiliary requests 1 and 2 - Art. 123(2) EPC**

1. Claim 1 of auxiliary requests 1 and 2 are each based on claim 7 as granted, with the following modifications:

   - *"Framework"* has been replaced by *"**Kabat** framework"*
   - The additional element *"... and wherein at least one of said amino acid substitution is also outside of the first heavy chain hypervariable loop as defined by Chothia et al. [Chothia and Lesk, J. Mol. Biol., 196:901-917 (1987)] ..."* has been added (this element will subsequently be abbreviated to read *"at least one AA outside Chothia"*).
   - Claim 1 of the second auxiliary request differs from claim 1 of the first auxiliary request in that only selection criterion (c) for the amino acids to be substituted is recited.

   Claims 2 - 14 in the first auxiliary request and claims 2 - 16 in the second auxiliary request were adapted correspondingly, with minor modifications in their wording.

   In the procedure, it became clear that some Opponents objected to the fact that the Proprietor has omitted to clarify whether the *"at least one AA outside Chothia"* feature should be considered to represent a limiting technical feature or a disclaimer. The following analysis takes into account both alternatives.

2. The *"at least one AA outside Chothia"* element as a limiting technical feature:

   A limiting technical feature must clearly have a basis in the application as originally filed, in order to comply with Art. 123(2) EPC.

   Taking into account the reasons set forth in the rejection of the main request under Art. 123(2) EPC, the Opposition Division is still of the opinion that no such basis exists.

Indeed, it is still considered that the only part of the application as filed which mentions the *Chothia* article (page 9/line 37 - page 10/line 9), and reading

> *"The variable regions of each light/heavy chain pair form the antibody binding site. The chains all exhibit the same general structure of relatively conserved framework regions joined by three hypervariable regions, also called CDRs (see, "Sequences of Proteins of Immunological Interest," Kabat, E., et al., U.S. Department of Health and Human Services, (1983); and Chothia and Lesk, J. Mol. Biol., 196:901-917 (1987), which are incorporated herein by reference)".*

is nothing more than an acknowledgement of prior art, as required by Rule 27(1)(b) EPC.

Even if it is assumed, *arguendo*, that by such acknowledgement, the teaching given by *Chothia* (i.e. that "his" hypervariable loop H1 extends from amino acid residues 26 - 32, contrasting with *Kabat's* definition of CDR1 as spanning residues 31 - 35) is incorporated into the application as filed, the latter does not contain any support whatsoever of the generalized teaching that any humanized immunglobulin prepared according to the methods of the application regularly must have *"at least one amino acid substitution ... outside of the first heavy chain hypervariable loop as defined by Chothia et al. [...]"*.

In fact, with regard to the observations already made in paragraph d6) above, the meaning attributed to the term "CDR" throughout the application as filed clearly follows *Kabat's* definition. For instance, the skilled person, looking at Fig. 1 depicting the heavy chain of the single exemplified antibody prepared according to the method of the patent, would not recognize anything more than the substitution of 2 amino acid residues at positions 27 and 30, **outside of the underlined *Kabat* CDR1**. From this unique example, either considered on its own or in conjunction with the body of the description, he/she could not derive the slightest indication that an alleged novel and inventive teaching resides in the regular substitution of an amino acid outside *Chothia's* hypervariable loop H1 extending from amino acid residues 26 - 32.

Hence, the addition of the *"at least one AA outside Chothia"* feature, when seen as a limiting feature, does not comply with the requirements of Art. 123(2) EPC.

3. The *"at least one AA outside Chothia"* feature as a disclaimer:

a) As seen by the Proprietor:

According to the submissions made by the Proprietor, the introduction of the said feature in claim 1 of the first and second auxiliary request meets the basic requirements for acceptability of a disclaimer:

- Firstly, the disclaimer format was considered to be appropriate, as no "positive limitation" could be used to express the alleged novel and inventive teaching that an amino acid outside of *Chothia's* hypervariable loop H1 extending from positions 26 - 32 should be substituted;

- Secondly, the subject-matter remaining in the claim after inclusion of the disclaimer was considered to be novel and inventive; claim 1 of the first and second auxiliary request were considered to provide a major novel and inventive teaching by reciting 3 specific criteria according to which amino acid substitutions should be made during humanization of immunoglobulins, which criteria are not to be found in the prior art as represented by **D36**. This would appear to be supported by **D40**, which in its conclusive statement as to the work achieved in **D36** (**D40**, page 17/right column/lines 3 - 7 and the last two sentences), defines a still unsolved technical problem; this problem is now claimed to be solved by the method of claim 1. Hence, **D36** was considered to become irrelevant for the purpose of assessing novelty and inventive step after inclusion of the disclaimer.

- Thirdly, the Proprietor argued that the scope of the disclaimer was commensurate in scope with the prior art to be disclaimed as it precisely removed **D36** from coverage, in which document the only amino acid substitutions made by *Riechmann et al.* were outside of *Kabat* CDRs (residues 31 - 35), but inside the first heavy chain hypervariable loop according to *Chothia* (residues 26 - 32), in contrast to the practical implementation of the alleged invention, where at least one amino acid substitution was to be made outside *Chothia* loop H1.

In this context, the Proprietor pointed to the fact that, on page 18/line 23, the application as originally filed already provided a supporting basis for the disclaimer, as it contained a reference to **D36**.

- Fourthly, following the EPO's usual approach to disclaimers, the prior art itself was considered to provide the relevant supporting basis under Art. 123(2) EPC; claims 1 of the first and second auxiliary request were therefore considered to be in line with Art. 123(2) EPC.

b) As seen by the Opponents:

All Opponents appeared to be in agreement that the *"at least one AA outside Chothia"* feature was unacceptable as a disclaimer and would contravene Art. 123(2) EPC for two main reasons:

- According to established case law such as given in T917/94, T863/96, T963/96, T645/96, a disclaimer is only allowable if the disclaimed document is completely removed from the relevant prior art after inclusion of the disclaimer, that is, if it represents an accidental disclosure. However, the Opponents considered **D36** to represent the closest state of the art available at the priority date of the application as filed. They argued that if the disclaimer would not be present in claim 1, the latter would not be novel and inventive with respect to **D36**, as already acknowledged by the Opposition Division in the preliminary opinion. Hence, the disclaimer would only appear to be included by the Proprietor in claim 1 to make its non-inventive teaching inventive, which clearly contravenes the principles set forth in T917/94 and T170/87.

- The *"at least one AA outside Chothia"* feature is not an appropriate disclaimer, as it does not disclaim the specific embodiment disclosed in **D36**, but a much broader teaching which has been extrapolated by the Proprietor from the specific teaching according to **D36** to render the subject-matter of his claim 1 novel and inventive. The Opponents therefore considered that the disclaimer in claim 1 of the first and second auxiliary request added an additional technical teaching to the claimed

method, which teaching was not derivable from the content of the application as originally filed. The disclaimer was not therefore be considered to be allowable under Art. 123(2) EPC. In this respect, reference was made to T245/91.

c) As seen by the Opposition Division:

In accordance with the case law of the Boards of Appeal, it would be allowable under Article 123(2) EPC to formulate a disclaimer which is precisely defined and limited to the prior art disclosure, provided this disclosure is an accidental novelty-destroying disclosure (T0863/96, paragraph 3.2 of the reasons).

c1) A disclaimer is only allowable if the prior document containing the excluded disclosure has no relevance for any further examination aspect of the claimed invention; upon introduction of the disclaimer, this prior document must disappear from the prior art field to be taken into consideration (T596/96, paragraph 2.2 of the reasons, and T863/96, paragraph 3.2 of the reasons).

In the present case, document **D36**, allegedly justifying the introduction of the disclaimer *"at least one AA outside Chothia"*, indisputably relates to the same field as the claimed invention, namely to the humanisation of an antibody by a CDR grafting method.

Moreover, the examination of all cited prior documents made during substantive examination and opposition phase has already revealed that document **D36**, together with its patent counterpart **D48**, is to be considered to represent the piece of prior art coming closest to the claimed subject-matter, as **D36** attempts to solve the problem of decreased affinity of a particular humanized antibody upon transfer of rat *Kabat* CDRs onto a human framework by substituting additional amino acids in the *Kabat* framework region. Hence, this document remains highly relevant with or without a disclaimer in claim 1. **D36** does not therefore represent an "accidental" anticipation.

The introduction of the *"at least one AA outside Chothia"* feature as a disclaimer into claim 1 does not therefore meet the requirements for allowability of a disclaimer under Art. 123(2) EPC as established by current case law.

c2) Assuming, arguendo, that **D36** would indeed be an accidental disclosure, the proposed disclaimer would not be allowable because, firstly, contrary to the Proprietor's assertion, it is not considered by the Opposition Division to have a basis in the application as originally filed and, secondly, it is not precisely defined and limited to the prior art disclosure:

- The reference to document **D36** on page 18/line 23 does not form part of the invention, but is nothing more than an acknowledgement of this document made in the context of preferred genetic engineering techniques. It was certainly not intended to exclude from the scope of the claims the humanized immunoglobulin and method for the production thereof according to **D36**.

- The Opposition Division cannot follow the Proprietor's interpretation that **D36** or its patent counterpart **D48** would disclose a particular approach for the preparation of humanized antibodies, which the Proprietor should be entitled to disclaim in his own claims, in which he clearly would recite a different method.

  As best seen in Fig. 1 of **D36**, *Riechmann et al.* disclose the synthesis of a humanized antibody against the CAMPATH-1 antigen, said antibody comprising the CDRs of rat antibody YTH 34.5HL on a human framework (derived from antibody NEW for the heavy chain and antibody REI for the light chain). Intentional Ser27 ---> Phe27 and Ser30 ---> Thr30 framework substitutions were made to restore the helper function in loop packing seen in most human heavy chains, thereby obtaining a significant increase in binding affinity for the CAMPATH-1 antigen in comparison to the humanized antibody having only the CDRs grafted (**D36**, page 326/left column/middle paragraph). As set forth by the Opposition Division in

paragraph **D.3** of its preliminary opinion dated 02/05/99, these 2 substitutions implicitly follow the "3 rules" of claim 1 of the first auxiliary request and claims 1 - 3 of the second auxiliary request. However, the following is noted:

- **D36** discloses the preparation of a specific humanized antibody and there is no explicit universal teaching which the authors conclude could be applicable to the preparation of other humanized antibodies. What the skilled person would learn from **D36** is simply that, in order to increase binding affinity, amino acid residues 27 and 30 of a particular human acceptor framework have been substituted for their rat counterparts. There is simply no indication in **D36** that further amino acid substitutions should be made **outside of a whole region**, as implied by the term *"at least one AA outside Chothia"*, which excludes amino acid residues 26 - 32 from the region of the immunoglobulin where *"at least one further amino acid substitution"* should be made.

- In the last sentence on page 326/left column/middle paragraph of **D36**, the authors observe that *"... alterations in the 'Kabat' framework regions can enhance the affinity of the antibody ..."* (underlining added), thereby indicating that their conclusion only applies to the anti-CAMPATH-1 antibody they have prepared. Even the section "Prospects" on page 327 of **D36** only relates to potential therapeutic implications of the same particular humanized anti-CAMPATH1 antibody.

- If some sort of generalized technical lesson can be learned from **D36**, it is that only the *Kabat* framework (hence, the portions of the immunoglobulin outside the *Kabat* CDRs) has been considered for experimental manipulation (*"... alterations in the 'Kabat' framework regions can enhance the affinity of the antibody ..."*, underlining added).

There is no mention whatsoever of any manipulation to be made *"... outside of the first heavy chain hypervariable loop as defined by Chothia et al. [Chothia and Lesk, J. Mol. Biol., 196:901-917 (1987)] ..."*. The statement given in **D36** on page 326,

*"By sequence, the first hypervariable loop extends from residues 31 - 35 (ref. 25 = **D27**), whereas by structure it extends from residues 26 - 32 (ref. 32 = **D28**)."*

is no more than an acknowledgement of prior art concepts of hypervariable loops, equivalent to what the inventors have done on page 9/line 37 - page 10/line 7 of the application as filed.

In the Opposition Division's view, the disclaimer introduced in claim 1 of the first and the second auxiliary request therefore comprises an unallowable generalization of the teaching according to **D36**.

Moreover, by applying such disclaimer, which does not recite what **D36** teaches, namely 2 amino acid substitutions at positions 27 and 30 in the heavy chain of a humanized anti-CAMPATH1 antibody, to a method for the production of **any** humanized antibody directed against **any** antigen, the Proprietor at the same time excludes from claim 1 a broad area of previously undisclosed subject-matter, and narrows it to technical embodiments which have a basis neither in the application as filed nor in **D36**.

The disclaimer in claim 1 of the first and the second auxiliary request does not comply with Art. 123(2) EPC, because it adds an additional technical teaching to the claimed method which was neither derivable from the content of the application as originally filed nor from **D36**.

## C Auxiliary request 3 - Art. 123(2) and (3) EPC

1. Claim 1 of the third auxiliary request substantially corresponds to claim 7 as granted, but includes the subject-matter of claim 10 as granted; hence claim 1 of the third auxiliary request relates to the production of a humanized immunoglobulin, wherein the mature heavy and light variable region sequences of the immunoglobulin obtained by the method have the exact amino acid sequence as given beneath the nucleotide sequences of Figures 3 and 4.

   Claims 2 - 13 were adapted correspondingly, with minor modifications in their wording.

2. Opponent 11 challenged the validity of claim 1 of the third auxiliary request under Art. 123(2) EPC by arguing that, owing to the controversial definition of CDRs throughout the application as filed, claim 1 would still cover embodiments which were not originally disclosed. More particularly, he pointed to the fact, that the application as filed would appear to use 2 divergent definitions of the Kabat CDR3 of the heavy chain, said to be composed of amino acid residues 95 - 102 on page 10/lines 3 - 5 (via the reference to *Kabat's* document **D15**), but being defined as comprising amino acid residues 99 - 106 on page 26/line 26.

   Moreover, in the view of Opponent 11, since the Proprietor had always used the combined *"Kabat + Chothia"* definition in his originally filed application (meaning that CDR1 of the heavy chain comprises amino acid residues 26 - 35), and since claim 1 of the third auxiliary request now would appear to relate to *Kabat* CDRs only (meaning that CDR1 of the heavy chain only comprises amino acid residues 31 - 35), the scope of the granted claims has been extended (Art. 123(3) EPC).

3. In reply, the Proprietor merely pointed out that claim 1 of the third auxiliary request was now limited to obtaining, by means of the claimed method, an immunoglobulin having the amino acid sequence as given beneath the nucleotide sequences in Figures 3 and 4, which were already included in the application as originally filed.

4. The Opposition Division fully appreciates the Proprietor's position. Claims 1 - 13 of the third auxiliary request have a clear basis in claims 11, 12, 19 and 22 as well as page 7/lines 20 - 33 and the complete section titled "Experimental" on pages 26 - 32 of the original application; indeed, by limiting its scope to the mature light and heavy chains as depicted in Figures 3 and 4, claim 1 now only covers the preparation of the humanized anti-*Tac* antibody as given in the single illustrative example of the application as filed.

As Figures 3 and 4 were already disclosed in the application as originally filed, claims 1 - 13 of the third auxiliary request clearly meet the requirements according to Art. 123(2) EPC.

Moreover, the scope of protection has not been extended (Art. 123(3) EPC), as claim 1 of the third auxiliary request corresponds to combined claims 7 and 10 as granted, with the additional limitation that the claimed mature light and heavy chain variable region protein sequences are **exactly** as given beneath the nucleotide sequences of Figures 3 and 4, and not *"homologous to"*, as recited in granted claim 10.

## D Auxiliary request 3 - Art. 84 EPC

1. Some of the Opponents raised objections as to the alleged unclear meaning of the terms *"rare"* and *"predicted"* in criteria (a) and (c) of claim 1. It was also argued that claims 1 - 13 of the third auxiliary request did not meet the requirement of conciseness as recited in Art. 84 EPC, because most of the claim wording was now superfluous with regard to the limitation of claim 1 to the exact amino acid sequences as given beneath the nucleotide sequences of Figures 3 and 4.

2. The Opposition Division agrees with the Proprietor's observation that objections under Art. 84 EPC can only be raised against an amended auxiliary request, if the alleged unclarities were caused by the amendments. Indeed, the terms *"rare"* and *"predicted"* were already used in criteria (a) and (c) of e.g. claim 7 as granted. It is also true that the Opponents have raised Art. 84 EPC objections in their initial notices of opposition against the said terms; however, objections made under Art. 84 EPC do not constitute a ground for opposition, and the Opposition Division

merely wishes to refer to the Proprietor's convincing statements refuting the Opponent's objections, submitted with his first letter dated 07/04/98, page 72/last paragraph - page 74/2nd paragraph.

As concerns the alleged superfluous use of a generic wording in claim 1 to recite a method which would appear to yield exactly one product, it should be emphasized that the Proprietor, by limiting claims 1 - 13 to the immunoglobulin having the amino acid sequence as given beneath the nucleotide sequences of Figures 3 and 4, has only defined the precise structure of the **end product** obtained by using the claimed method. However, the method of claim 1 still has more than one degree of freedom insofar as the choice of **starting products** is concerned. Indeed, the "starting antibodies" are not defined in claim 1, and by selecting different human acceptor and different non-human donor antibodies and applying the 3 criteria for CDR and additional amino acid grafting as set forth in claim 1, one may still arrive at a humanized immunoglobulin wherein the mature light and heavy chain variable region protein sequences are as in Figures 3 and 4 (see also page 17/lines 28 - 35). It should also be borne in mind that claim 1 does not impose structural limits on the sequence of the constant regions of the final immunoglobulin.

The Opposition Division therefore considers the wording used in claims 1 - 13 of the third auxiliary request to be commensurate with the scope of protection sought.

## E Auxiliary request 3 - Art. 54 EPC

1. In the view of Opponent 11, since the Proprietor had always used the combined *"Kabat + Chothia"* definition in his originally filed application (meaning that CDR1 of the heavy chain comprises amino acid residues 26 - 35), and since claim 1 of the third auxiliary request now would appear to relate to *Kabat* CDRs only (meaning that CDR1 of the heavy chain only comprises amino acid residues 31 - 35), the latter would not appear to enjoy the priority dates of either the first (PDL1 application US290975, 28/12/88) or second priority application (PDL2 application US310252, 13/02/89). The effective date for the claims of the third auxiliary request would therefore be the filing date 28/12/89.

Hence, document **D52**, allegedly made available to the public on 27/12/89, and being the counterpart of the disputed patent published in the scientific literature, would destroy the novelty of the claims according to the third auxiliary request, as Fig. 2 of **D52** was identical to Figures 3 and 4 of the application as filed.

2. However, in the analysis of entitlement to priority of claim 7 made in its preliminary opinion annexed to the invitation to Oral Proceedings, the Opposition Division has acknowledged that the only instance where the application of criteria (a), (b) and (c) of granted claim 7 for the design of a humanized immunoglobulin has been described, was in the part entitled "EXPERIMENTAL", more particularly pages 21ff of PDL1. This portion of the PDL1 application is **identical** with pages 26 - 32 of the application as filed and relates **exactly** to the preparation of the anti-*Tac* antibody which is now recited (by reference to the amino acid sequences of Figs. 3 and 4) in claim 1 of the third auxiliary request. As this claim 1 substantially corresponds to combined claims 7 and 10 as granted, and since Figs. 3 and 4 of the application as filed correspond to Figs. 1 and 2 of the PDL1 application, it follows that claim 1 of the third auxiliary request enjoys the priority date of the PDL1 application US290975, 28/12/88. **D52** does not therefore belong to the state of the art as defined in Art. 54(2) and (3) EPC and the Opponent's objection are without substance.

As none of the further documents cited by the Opponents discloses immunoglobulins having mature light and heavy chain variable region protein sequences as given beneath the nucleotide sequences of Figures 3 and 4, the subject-matter of claims 1 - 13 of the third auxiliary request is novel.

## F Auxiliary request 3 - Art. 56 EPC

1. The main objection raised by some of the Opponents was based on document **D11**, which describes the original murine monoclonal anti-*Tac* antibody used in the CDR grafting method of the patent (see page 2/lines 5 - 15 of the application as filed). Later, as it became clear that an IL-2 receptor binding monoclonal antibody such as the anti-*Tac* antibody of **D11** would have considerably useful therapeutic properties, the skilled person wishing to humanize it would come across document **D32** which discloses the basic technique of CDR grafting, i.e. the transfer of non-human CDRs onto a human antibody acceptor framework. When following the additional teaching given by **D32** that, in order to obtain a functional unaltered antibody,

> *"..., it may be necessary only to transfer those residues which are accessible from the antigen binding site, **and this may involve transferring framework region residues as well as CDR residues.**"*
>
> ***D32**, page 7, 4th paragraph*

the skilled person would obviously try to replace certain critical amino acids in the human acceptor framework by the corresponding non-human donor amino acids and therefore obtain a humanized immunglobulin similar to the antibody of claim 1; the latter was not considered by the Opponents to exhibit outstanding or unexpected properties, as the tests described in the patent revealed that it had lost 2/3 of its affinity in comparison with the unaltered murine anti-*Tac* antibody.

2. In reply, the Proprietor pointed to the fact that, by virtue of the limitation of claim 1 to the mature light and heavy chain variable region protein sequences as given beneath the nucleotide sequences of Figures 3 and 4, claim 1 related to a method wherein 15 independent amino acid substitutions had been made in the construction of the particular humanized anti-*Tac* antibody. For the purposes of assessing whether this claim would involve an inventive step, it should be evaluated whether it was obvious to try to replace such a number of independent amino acids in a single antibody according to three criteria which allegedly had been developed by the inventors, taking into account the case law established in numerous decisions of the Boards of Appeal relating to the issue "reasonable

expectation of success" (e.g. in T60/89). He also noted that, if the Opposition Division considered auxiliary requests 1 and 2 to be inadmissible under Art. 123(2) EPC because of the limited teaching given by **D36** (see paragraph **B.**,4., c1) above), the inventors would have needed 15 times the luck the authors of **D36** had, when they obtained a humanized antibody having increased affinity by the substitution of 1 amino acid in the *Kabat* framework.

3. As already set forth above, the subject-matter of claim 1 consists of a method for the preparation of a humanized immunoglobulin, wherein in addition to the step of grafting CDRs from a donor to an acceptor antibody, certain additional amino acids in the acceptor framework are substituted according to criteria (a) - (c), **and wherein the mature light and heavy variable region protein sequences of the thus humanized immunoglobulin have the amino acid sequence as given beneath the nucleotide sequences of Figures 3 and 4.**

Hence, although the wording of claim 1 gives the impression that a generic method is claimed, it is nevertheless limited to the case where an application of the recited method yields a unique immunoglobulin having an exact amino acid sequence in the variable regions of both the heavy and light chain. The said exact definition is based in Figures 3 and 4 which depict the nucleotide sequence of the heavy and light chain variable region gene of the humanized anti-Tac antibody prepared according to the experimental part of the patent, together with the translated amino acid sequence for the part of the gene encoding protein.

The two entities from which the said humanized antibody has been derived, namely the murine anti-*Tac* donor and the human acceptor antibody *Eu*, are shown in Figures 1 and 2. From the combination of Figs. 1/2 with Figs. 3/4, it is clearly recognizable that 12 amino acids at *Kabat* positions 27, 30, 48, 67, 68, 93, 95, 98, 106 - 108 and 110 of the heavy chain and 3 amino acids at *Kabat* positions 47, 59 and 62 have been substituted in the human *Eu* antibody for their murine anti-*Tac* counterparts.

a) With regard to the purely structural aspect, the nearest prior art document is represented by **D15**, wherein *Kabat* gives the amino acid sequences of both the heavy and the light chain of the human *Eu* antibody. The difference between **D15** and the humanized antibody produced by the method of claim 1 resides in the fact that the CDRs and 15 additional amino acids have been transferred from the murine anti-*Tac* antibody according to **D11**. The said difference accounts for the obtaining of a humanized immunoglobulin still having substantial affinity for its cognate antigen, the IL-2 receptor, while exhibiting negligible immunogenicity in human patients (HAMA response); under its commercial trade name ZENAPAX®, it was the first clinically approved humanized antibody anywhere, proven to exhibit highly desirable therapeutic properties (see e.g. documents **D112**, **D119**, **D120** by the Proprietor).

The objective problem to be solved is therefore the provision of a humanized immunoglobulin having improved therapeutic properties.

The solution provided is the humanized immunoglobulin prepared according to the method of claim 1 of the third auxiliary request, wherein 15 additional amino acids at specific positions in the human heavy and light chain variable regions have been replaced by their murine counterparts.

None of the many documents cited during the opposition phase contributes to the solution provided, as none of them contains a suggestion pointing to **the substitution of exactly 15 amino acids (not 14, not 16) at *Kabat* positions 27, 30, 48, 67, 68, 93, 95, 98, 106 - 108 and 110 of the *Eu* heavy chain and at *Kabat* positions 47, 59 and 62 of the *Eu* light chain (and not at any other position)**.

**D11**, disclosing the murine anti-*Tac* antibody does not mention humanized antibodies, and as best seen from **D40**, an article reviewing the state of the art in the field of antibody engineering in 1988, and referencing e.g. the publications of Kabat (**D27**), Chothia (**D28**), Roberts (**D31**), Amit (**D23**), Verhoeyen (**D37**) and Riechmann (**D36**), none of these publications or the

*Winter* patent (**D32**) discloses the preparation of a humanized immunoglobulin based on the human *Eu* / murine anti-*Tac* combination.

The subject-matter of claim 1 of the third auxiliary request and claims 2 - 13, being dependent upon or referring to claim 1, therefore involves an inventive step.

b) Starting from the functional aspect involved in the method of claim 1, that is, only taking into account the mere fact that apart from the CDRs, some extra amino acids have to be transferred from the donor to the acceptor molecule, the nearest prior art document is represented by **D36**, disclosing the synthesis of a humanized antibody against the CAMPATH-1 antigen, said antibody comprising the CDRs of rat antibody YTH 34.5HL on a human framework (derived from antibody *NEW* for the heavy chain and antibody *REI* for the light chain). Intentional Ser27 ---> Phe27 and Ser30 ---> Thr30 framework substitutions were made to restore the helper function in loop packing seen in most human heavy chains, thereby obtaining a significant increase in binding affinity for the CAMPATH-1 antigen in comparison to the humanized antibody having only the CDRs grafted (**D36**, page 326/left column/middle paragraph).

The difference between **D36** and the humanized antibody produced by the method of claim 1 resides in the fact that the latter is based on a human *Eu* / murine anti-*Tac* combination of acceptor / donor antibodies instead of human *NEW* or *REI* / rat YTH 34.5HL as used in **D36** and in that a total of 15 additional amino acids have been transferred from the donor to the acceptor antibody to obtain the desired humanized immunglobulin, instead of only 2 in the case of the antibody according to **D36**.

As in paragraph a) above, the said difference accounts for the obtention of a humanized immunoglobulin still having substantial affinity for its cognate antigen, the IL-2 receptor, while exhibiting negligible immunogenicity in human patients (HAMA response); under its commercial trade name ZENAPAX®, it has been the first clinically approved humanized antibody anywhere, proven to exhibit highly desirable therapeutic properties (see e.g. documents **D112**, **D119**, **D120** by the Proprietor).

The objective problem to be solved is therefore the provision of a universally applicable set of rules for the reproducible selection of additional amino acid residues to be substituted in the preparation of **any** humanized antibody, in extension of the conclusion reached by the authors of **D36** in the context of a particular humanized immunoglobulin, that

> *"... alterations in the Kabat framework can enhance the affinity of the antibody."*
> ***D36**, page 326/left column/last of middle paragraph*

The solution provided is the humanized immunoglobulin prepared according to the method of claim 1 of the third auxiliary request, wherein 15 additional amino acids at specific positions in the human heavy and light chain variable regions have been replaced by their murine counterparts, following selection criteria (a) - (c).

None of the many documents cited during the opposition phase contributes to the solution provided, as none of them contains a suggestion pointing to the technical features recited in selection criteria (a) - (c), **the application of such criteria to the humanisation of an anti-*Tac* antibody leading to the substitution of exactly 15 amino acids (not 14, not 16) at *Kabat* positions 27, 30, 48, 67, 68, 93, 95, 98, 106 - 108 and 110 of the *Eu* heavy chain and at *Kabat* positions 47, 59 and 62 of the *Eu* light chain (and not at any other position).**

As already argued in the context of Art. 123(2) EPC, the Opposition Division considers that the 2 substitutions made by *Riechmann et al.* in **D36** implicitly follow at least 2 of the "3 rules" of claim 1; however, **D36** discloses the preparation of a **particular** humanized antibody and there is no explicit universal teaching which the authors conclude could be applicable to the preparation of other humanized antibodies. What the skilled person would learn from **D36** is simply that, in order to increase binding affinity, amino acid residues 27 and 30 of a particular human acceptor framework have been substituted for their rat counterparts. The authors of **D36** were not aware of the fact that their substitution strategy could be formulated in a more generic manner to yield substitution 3 criteria (a) - (c) according to claim 1 of the third

auxiliary request. Hence, they neither proposed that a similar strategy could be used when attempting to humanize other antibodies, nor that further amino acid substitutions deep in the *Kabat* framework should be made.

While it is true that the publications of Chothia (**D28**), Roberts (**D31**), Amit (**D23**), Verhoeyen (**D37**), Cheetham (**D40**) and Winter (**D32**), in the wider context of engineering the antigen binding site and maintaining or improving antibody affinity, identify potential problems with some particular amino acids in the *Kabat* framework, none of them provides a universal solution by formulating substitution rules similar to the 3 criteria (a) - (c) of claim 1 and suggesting that such rules could be employed in antibody humanisation.

Most importantly, none of the cited documents suggests that **exactly 15 amino acids (not 14, not 16) at *Kabat* positions 27, 30, 48, 67, 68, 93, 95, 98, 106 - 108 and 110 of the *Eu* heavy chain and at *Kabat* positions 47, 59 and 62 of the *Eu* light chain (and not at any other position)** should be made in order to successfully apply the method as defined by criteria (a) - (c) to the preparation of the humanized anti-*Tac* antibody of claim 1.

The subject-matter of claim 1 of the third auxiliary request and claims 2 - 13, being dependent upon or referring to claim 1, therefore involves an inventive step.

## G Rejection of the Proprietor's request to submit another auxiliary request during oral proceedings

In view of the complexity of the case and the number of parties involved, the Opposition Division, in its preliminary opinion annexed to the invitation to attend Oral Proceedings, has set a time limit of 3 months to make written submissions in preparation of the oral proceedings (Rule 71a(1) EPC). On 17/12/99, i.e. 3 days before the expiry of the above time limit, the Proprietor has filed 5 auxiliary requests, together with new supporting documents **D112 - D129**.

Clearly, the Opponents did not have time to file their comments on the 5 auxiliary requests within the time limit set under Rule 71a(1) EPC, but the Opposition Division considered that the period of 3 months still available before the date of the Oral Proceedings would provide them with a fair opportunity to prepare such comments for oral submission.

Nevertheless, further substantial observations, partly on the preliminary opinion issued by the Opposition Division and partly on the letter of the Proprietor dated 17/12/99, were submitted by Opponent 4 on 16/12/99, the submission introducing further documents **D130 - D134** as listed in Annex A, and Opponent 8 on 17/12/99, 08/03/00 and 13/03/00, the submission introducing further documents **D135 - D141** as listed in Annex A.

With a letter dated 16/03/00 (that is, **4 days before the date of the oral proceedings**), the Proprietor submitted a new set of 3 auxiliary requests, wherein auxiliary requests 1 and 2 were derived from auxiliary requests 3 and 4 as filed on 17/12/99 and auxiliary request 3 was identical with auxiliary request 5 as filed on 17/12/99. The submission was said to be caused by an effort to overcome a novelty objection made by Opponent 8 and being based on an alleged early publication date of document D52.

At this point of the proceedings, and although the Proprietor asserted that a simplification of the procedure had been obtained by the reduction in the number of auxiliary requests, the amendments carried out in the wording of the claims (such as the replacement of *"framework"* by *"**Kabat** framework"*) were already

considered by the Opposition Division to place a heavy burden on the Opponents insofar as they possibly had to substantially modify their argumentation shortly before the oral proceedings, taking into account that the meaning attributed to terms such as *"Kabat CDRs"*, *"Kabat framework"* or *"Chothia loops"* were absolutely critical in the evaluation of the merits of the contested patent.

Nevertheless, in the opening phase of the Oral Proceedings, none of the Opponents lodged a protest against the acceptance by the Opposition Division of late filed auxiliary requests 1 - 3.

After rejection of the main request as well as auxiliary requests 1 and 2 for non-compliance with Art. 123(2) EPC, the Proprietor requested the Opposition Division to set forth the exact reasons for the rejection; he furthermore requested an opportunity to file another auxiliary request which would take into account the said reasons. The Proprietor argued that he could not have reasonably have foreseen that auxiliary requests 1 and 2 would be rejected under Art. 123(2) EPC.

In reply, some of the Opponents announced that, should the Opposition Division be inclined to accept the Proprietor's requests, they would seek an adjournment of the Oral Proceedings and an award of costs.

The Opposition Division decided to refuse the Proprietor's request for filing another auxiliary request **as being a late filed request**, for the following reasons:

- By having filed his first set of 5 auxiliary requests shortly before expiry of the time limit set under Rule 71a(1) EPC, the Opponents were deprived of the opportunity to file comments thereon within the said time limit.

- The Proprietor had sufficient opportunity to file auxiliary requests suitable to overcome the grounds of opposition put forward by the Opponents. Acceptance of the last 3 auxiliary requests filed 4 days before the oral proceedings by the Opposition Division (and apparently also by the Opponents) is already considered to constitute a benevolently granted supplementary opportunity for the Proprietor to defend his position.

- No further request was presented at the opening phase of the Oral Proceedings.

- It is neither usual in Oral Proceedings for an Opposition Division to proclaim the exact reasons for the rejection of a particular request nor is it common practice to grant a party sufficient time to formulate an auxiliary request which takes into account each and every such reason in order to finally obtain an allowable request overcoming all objections raised.

- For reasons of fairness, the Opponent's request for postponement of the Oral Proceedings, should the Proprietor's request be allowed, would have to have been accepted, in order to give them the necessary time to study the amendments proposed. With regard to the number of Opponents involved, such a postponement would have caused an unacceptable delay of the procedure.

- After rejection of the first and second auxiliary requests, there was still a third auxiliary request on the table which had not been discussed. Hence, the rejection by the Opposition Division of the previous auxiliary requests did not automatically lead to the revocation of the patent.

## III. Decision

- For the reasons given above, the Opposition Division considers that neither claim 1 of the main request, nor claim 1 of the first or claim 1 of the second auxiliary request meet the requirements according to Art. 123(2) EPC.

- *Obiter dictum*, the disclaimer introduced in claim 1 of the first and claim 1 of the second auxiliary request, *"at least one AA outside Chothia"* does not comply with the established case law of the EPO's Boards of Appeals on the allowability of disclaimers..

- Claims 1 - 13 of the third auxiliary request have a clear basis in the application as originally filed; their scope has not been extended over the scope of the claims as granted; the said claims therefore comply with the requirements according to Art. 123(2) and (3) EPC.

- Claims 1 - 13 of the third auxiliary request meet the requirements according to Art. 84 EPC.

- Claims 1 - 13 of the third auxiliary request meet the requirements according to Art. 54 EPC, since their respective subject-matter is not disclosed in the available prior art documents.

- Claims 1 - 13 of the third auxiliary request meet the requirements according to Art. 56 EPC, since their respective subject-matter is not obviously derivable from any of the available prior art documents, taken alone or in combination.

- The Proprietor's request for filing a further auxiliary request during oral proceedings is refused.

According to Art. 102(3) EPC, the patent is therefore maintained on the basis of claims 1 - 13 of the third auxiliary request, pages 1, 2, 4, 6 and 8 - 13 of the patent specification, pages 3, 5 and 7 of the adapted description as filed with the letter dated 12/06/00, and Figures 1 - 10 of the patent specification.